REMARKS

Status of the Claims

Claims 8, 9, 14, 15, 20, 21 and 32 are pending in the application. Claims 8, 9, 14, 15, 20, 21 and 32 are rejected.

Claim 15 is amended and claims 20 and 21 are canceled herein. No new matter is added to these claims.

Claim Amendments

Claim 15 is amended to overcome the 35 U.S.C §112, first paragraph rejection of the Final Office Action, mailed May 31, 2006 and maintained in the Advisory Action, mailed October 13, 2006. The claim is amended to incorporate the limitation of canceled claim 21. Thus, amended claim 15 is directed to a method of inhibiting tumor growth, inflammation and/or angiogenesis in a patient. This method comprises administering to the patient an antibody directed against a sequence consisting of SEQ ID No. 41 or a sequence consisting of SEQ ID No. 2 that is derived from a cell surface vascular endothelial growth factor and type I collagen inducible protein (VCIP) consisting of SEQ ID No. 13. Such an antibody blocks binding of $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ integrins to the cell surface vascular endothelial growth factor and type I collagen inducible protein, thereby inhibiting tumor growth, inflammation and/or angiogenesis in the patient (see Examples 15-29).

In the Advisory Action mailed October 13, 2006, the Examiner states that the claim amendments in response to the Final Office Action will be entered. However, the amendments failed to overcome some of the claim rejections of the Final Office Action, mailed May 31, 2006. Specifically, the Examiner maintains the following rejections:

Claim 15 stands rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Applicant respectfully traverses this rejection.

The Examiner states that the instant specification teaches a method of treating inflammation or angiogenesis and not a method of treating any pathological condition caused by integrin mediated cell-cell interaction. Additionally, the Examiner states that the instant invention teaches that the peptide was derived from human VCIP of SEQ ID No: 14. Hence, the Examiner maintains the rejection of claim 15 for lack of enablement.

Claim 15 is amended as discussed supra and is directed to a method of inhibiting tumor growth, inflammation and/or angiogenesis in a patient. The instant specification teaches that growth factors and inflammatory cytokines induced expression of VCIP (Example 12). The instant invention investigated the mechanism contributing cell-cell interaction in the above-mentioned cells and demonstrated that the cell-cell interaction was integrin mediated and that VCIP-RGD acted as a cell-associated integrin ligand (Example 15-18). Thus, the integrin mediated cell-cell interaction involving VCIP could also contribute to inflammation. The instant invention also investigated the contribution of VCIP-RGD in adhesion of

endothelial cells to extracellular matrix (Example 19). The instant invention further demonstrates that VCIP was co-expressed along with vWF and αvβ3 in the tumor vasculture (Example 20).

With regards to angiogenesis, the highly motile behavior of activated endothelial cells is known in the art to be crucial for angiogenesis. Since sprouting of new blood vessels requires cell division in preformed endothelial tissues (for instance, wall of the blood vessel) that is accompanied by migration of the endothelial cells, unnecessary angiogenesis can be prevented by inhibiting the migratory behavior of the endothelial cells (page 40, lines 25-30). The instant invention examined the role played by VCIP in the endothelial cell migration and angiogenesis by performing *in vitro* assays (Example 21-26) that are considered in the art to correlate with the results that one might expect to see *in vivo*. Mouse model (in vivo) was used to demonstrate that VCIP potentiated tumor growth by promoting tumor angiogenesis and augmented tumor metastasis (Examples 27-29). The instant invention demonstrated that anti-VCIP antibody blocked angiogenesis by inhibiting the formation of new capillaries *in vitro* (Example 29).

Applicant respectfully disagrees with the Examiner's argument that sequence of VCIP from which the peptides of SEQ ID NO: 2 and 41 are derived is SEQ ID NO: 14. Applicant reiterates that the instant invention demonstrated that incubation of cells (HEK293) expressing wild type VCIP with peptides that comprised RGD motif or with anti-VCIP-RGD antibody generated using the peptide of SEQ ID No. 2 inhibited cell-cell interaction (Example 14; Table 1). The peptide with SEQ ID No. 2 comprises amino acids 173-192 of the VCIP with SEQ ID No.

13. The VCIP with SEQ ID No. 14 just represents the phosphatase domain of human VCIP. This phosphatase domain comprises amino acids 145-161 of the VCIP with SEQ ID No. 13 and does not include the RGD domain. Hence, the peptide with SEQ ID NO. 2 and SEQ ID No. 41 cannot be derived from VCIP with SEQ ID No. 14. Therefore, Applicant has identifed VCIP in the instant claims as the one with SEQ ID No. 13.

Applicant submits that the claim amendments presented herein and the teachings in the instant specification with regard to claim amendments and sequence of human VCIP from which the peptides are derived satisfy the requirements of 35 U.S.C. §112, first paragraph. Thus, the scope of the claimed invention is commensurate with the scope of enablement provided. Accordingly, based on the claim amendments and remarks, Applicant respectfully request the withdrawal of rejection of claim 15 under 35 U.S.C. §112, first paragraph.

Claims 8-9 and 14 stand rejected under 35 U.S.C. §102(b) as being anticipated by **Vassilev** *et al* (Blood 1999 Jun 1; 93(11):3624-3631) as is evidenced by **Bendayan** (J Histochem Cytochem 1995, 43:881-886). Applicant traverses this rejection.

The Examiner finds the arguments made by the Applicant in the Response After Final non-persuasive. The Examiner states the referenced antibody was not raised against the peptide of 10 amino acid in length but purified by said peptide. The Examiner further states that the **Vassilev** *et al* teach that binding of anti-RGD antibodies to the peptide and to proteins expressing RGD sequence by

ELISA (page 3625, 1st col.). Additionally, the Examiner states that the referenced antibody were able to bind fibronection, fibrinogen, vitronection, VWF and laminin in a dose dependent manner. Based on this, the Examiner states that the skilled in the art would expect that the referenced antibody to bind to the sequences of SEQ ID NO: 2, 41 and 13. Hence, the rejection is maintained.

Applicant respectfully disagrees with the Examiner's reasons for maintaining the rejection. Independent claim 8 recites a method of inhibiting cell-cell interaction by contacting the cells with an antibody directed to specific peptides (SEQ ID No: 2 and SEQ ID NO: 41). **Vassilev** *et al* teach that the antibody was directed against a 10-amino acid peptide containing the RGD motif (page 3624, 2nd col., line 31-35). Although the peptide of **Vassilev** *et al* and those of the instant invention comprise the Arg-Gly-Asp sequence, the rest of the amino acids within these peptides are different. Hence, the peptides differ not only in the number of amino acid residues but also in the type of amino acids. The teaching in **Vassilev** *et al* of the ability of the antibody to bind fibronection, fibrinogen, vitronection, VWF and laminin in a dose dependent manner is inconsequential. That is, **Vassilev** *et al* do not teach that the antibody was also directed against the specific 5-amino acid peptide (SEQ ID No. 41) or the specific 20 amino acid peptide (SEQ ID No. 2) of the instant invention.

In order to anticipate a claim, the prior art reference must teach each and every element of the claim (M.P.E.P. 2131). Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient (M.P.E.P. 2112). Since the

instantly claimed method uses an antibody directed to the "specific peptides", whether an antibody generated against these peptides would block the binding of integrins to cell surface VCIP is not inherent based on the teachings of the references cited by the Examiner. Hence, independent claim 8 and its dependent claims 9 and 14 are not anticipated by **Vassilev** *et al.* Accordingly, based on the claim amendments and above-discussed remarks, Applicant respectfully requests the withdrawal of rejection of claims 8-9 and 14 under 35 U.S.C. §102(b).

Claims 15, 20-21 and 32 stand rejected under 35 U.S.C §103(a) as being unpatentable over **U.S. Patent No. 5,807,819** in view of **U.S. Patent No. 5,567,440** and **Vassilev** *et al* as is evidenced by **Bendayan**. Applicant respectfully traverses this rejection.

The Examiner finds Applicant's arguments made in the Response After Final unpersuasive. Specifically, the Examiner states that there is no need for motivation to make an antibody to either SEQ ID No: 2 or 41 because **Vassilev's** antibodies would bind the claimed sequences. The Examiner further states that in order to be prima facie obvious, one would have to substitute the CRGDDVC cyclic peptide taught by the **'819** patent with anti-RGD antibody taught by **Vassilev** *et al* in a method of inhibiting angiogenesis in a subject to arrive at the claimed invention.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or to combine the teachings. Second, there must be reasonable expectation of success. Finally, the prior art reference (or

references when combined) must teach or suggest all claim limitations (M.P.E.P. 2143).

Claim 15 is amended as discussed supra. In order to inhibit tumor formation, inflammation and/or angiogenesis, the antibody should bind peptides with SEQ ID NO: 2, SEQ ID NO: 41 or SEQ ID NO: 13. Such an antibody blocks binding of αvβ3 and/or α5β1 integrins to the cell surface vascular endothelial growth factor and type I collagen inducible protein. **Vassilev** *et al* teach that their antibody is directed against the 10 amino acid peptide and binds fibronection, fibrinogen, vitronection, VWF and laminin. There is clearly no teaching or suggestion in the **Vassilev** *et al* of the ability of the antibody to bind the "instant peptides" and in the ability of the antibody to block binding of αvβ3 and/or α5β1 integrins to the cell surface vascular endothelial growth factor and type I collagen inducible protein. Hence, the prior art references combined do not teach or suggest all claim limitations and provide no incentive to a person having ordinary skill in this art.

With regard to Examiner's argument that the antibody taught by **Vassilev** *et al* would bind the claimed sequences, Applicant would like to respectfully point out that the antibody of **Vassilev** *et al* binds a peptide with an amino acid sequence that differs from the instant peptides in number and type. In other words, the peptide of **Vassilev** *et al* is very different from that of the instant invention. Further, there is no demonstration in **Vassilev** *et al* of the antibody binding to the "instant peptides" nor has the Examiner provided any scientific evidence to support such binding. Thus, the antibody useful in the instantly claimed

method is not the same as taught by **Vassilev** *et al*. Hence, one cannot merely substitute the antibody taught by **Vassilev** *et al* and use it in the instantly claimed method to inhibit angiogenesis. Accordingly based on the claim amendments and above-mentioned remarks, Applicant respectfully requests the withdrawal of rejection of claims 15, 20-21 and 32 under 35 U.S.C §103(a).

This is intended to be a complete response to the Advisory Action, mailed October 13, 2006 and supplemental to the Final Office Action, mailed May 31, 2006. Applicants submit that the pending claims are in condition for allowance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Nov 30, 2006

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
Tel: 713-270-5391
Fax: 713-270-5361
badler1@houston.rr.com

Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant